Extracellular Vesicles for the Treatment of Radiation-Induced Normal Tissue Toxicity in the Lung.

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Public Summary:
Human stem cell-derived extracellular vesicles (EV) provide many advantages over cell-based therapies for the treatment of functionally compromised tissue beds and organ sites. Here we sought to determine whether human embryonic stem cell (hESC)-derived EV could resolve in part, the adverse late normal tissue complications associated with exposure of the lung to ionizing radiation. The hESC-derived EV were systemically administered to the mice via the retro-orbital sinus to explore the potential therapeutic benefits following exposure to high thoracic doses of radiation (14 Gy). Data demonstrated that hESC-derived EV treatment significantly improved overall survival of the irradiated cohorts ($P < 0.001$). Increased survival was also associated with significant reductions in lung fibrosis as quantified by CBCT imaging ($P < 0.01$, 2 weeks post-irradiation). Qualitative histological analyses revealed reduced indications of radiation induced pulmonary injury in animals treated with EV. EV were then subjected to a rigorous proteomic analysis to ascertain the potential bioactive cargo that may prove beneficial in ameliorating radiation-induced normal tissue toxicities in the lung. Proteomics validated several consensus exosome markers (e.g., CD68) and identified major classes of proteins involved in nuclear pore complexes, epigenetics, cell cycle, growth and proliferation, DNA repair, antioxidant function, and cellular metabolism (TCA cycle and oxidative phosphorylation, OXYPHOS). Interestingly, EV were also found to contain mitochondrial components (mtDNA, OXYPHOS protein subunits), which may contribute to the metabolic reprograming and recovery of radiation-injured pulmonary tissue. To evaluate the safety of EV treatments in the context of the radiotherapeutic management of tumors, mice harboring TC1 tumor xenografts were subjected to the same EV treatments shown to forestall lung fibrosis. Data indicated that over the course of one month, no change in the growth of flank tumors between treated and control cohorts was observed. In conclusion, present findings demonstrate that systemic delivery of hESC-derived EV could ameliorate radiation-induced normal tissue complications in the lung, through a variety of potential mechanisms based on EV cargo analysis.

Scientific Abstract:
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